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Prevalence of eosinophilic esophagitis in patients with refractory gastro-esophageal reflux disease symptoms

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Abstract: Background and Aim: Eosinophilic esophagitis is an inflammatory disorder of the esophagus that is being increasingly diagnosed in the adult population. The present study aimed to determine the prevalence of eosinophilic esophagitis among Egyptian patients presenting with refractory GERD symptoms. Methods: 40 consecutive adult Egyptian patients with refractory GERD symptoms were enrolled in the study. Upper GIT endoscopy was done for all participants with at least 3 biopsies taken from 2 different sites in the esophagus including the distal and either mid or proximal esophagus even if the esophagus appeared endoscopically normal. Gastric and duodenal biopsies were also taken along with esophageal biopsies. All biopsies were examined histopathologically by blinded gastrointestinal pathologists. An esophageal eosinophilic count $\geq$ 15/HPF, along with normal gastric and duodenal biopsies, substantiated the diagnosis of eosinophilic esophagitis. Results: The prevalence of eosinophilic esophagitis in this cohort was 2.5% (1/40). The affected participant was a 27 year old female patient who had a history of bronchial asthma (type 1 hypersensitivity reaction) for which she was treated with ,on demand, inhaled bronchodilators (short acting β agonist). The endoscopic examination of the affected participant showed furrows and plaques which are strongly suggestive of eosinophilic esophagitis. Conclusion: the low prevalence rate of eosinophilic esophagitis among the current small cohort of Egyptian patients with refractory GERD symptoms strongly mandates the search for additional data concerning the indications for esophageal biopsy in this subset of patients. History of atopy may warrant suspicion of eosinophilic esophagitis in this subset of patients.

Keywords: Eosinophilic, Esophagitis, Refractory, GERD

1. Introduction

Eosinophilic esophagitis is increasingly being recognized in adults and pediatric populations either as a separate entity or as a part of the spectrum eosinophilic gastroenteritis [1]. In adults, eosinophilic esophagitis can present in the third or fourth decades of life and various studies implicate it to be more predominant in men [2].

Eosinophilic esophagitis is an increasingly common diagnosis in patients with refractory Gastro-esophageal Reflux Disease (GERD). Patients with eosinophilic esophagitis are usually young men, present with a history of intermittent solid food dysphagia, and often have a history of food impaction. Most of these patients carry an underlying diagnosis of GERD [3, 4]. Markowitz et al found that 15 % of patients initially suspected of having GERD were actually discovered to have eosinophilic esophagitis [5]. Some data suggest that the condition is precipitated by foods and aeroallergens that stimulate a type 2 T-helper cell cytokine response [6]; whereas other data suggest that some patients have an atypical variant of GERD[7,8].

The diagnosis of eosinophilic esophagitis is made by demonstrating an abnormal number of eosinophils per high-power field (HPF) on a biopsy of esophageal mucosa [9, 10]. A range (15–30) of eosinophil counts has been used to establish the diagnosis of eosinophilic esophagitis, and some groups have advocated a combination of a clinical and histologic definition for eosinophilic esophagitis [11]. The First International Gastrointestinal Eosinophilic Research Symposium (FIGERS) came up with comprehensive guidelines regarding the diagnostic criteria for eosinophilic esophagitis. Accordingly, an esophageal eosinophilic count more than or equals to 15/HPF, along with normal gastric and duodenal biopsies, can substantiate the diagnosis of eosinophilic esophagitis. Moreover, patients must have biopsies after 6-8 weeks of twice daily acid suppression with proton pump inhibitors (PPI), or have a

negative PH study results in order to correctly diagnose eosinophilic esophagitis [11].

Eosinophilic esophagitis has been reported in all races; however, there has been no evidence to support an association with one particular race [12]. The present study aimed to determine the prevalence of eosinophilic esophagitis among Egyptian patients presenting with refractory GERD symptoms.

2. Patients and Methods

This study was conducted in the Gastroenterology and Hepatology Unit, Internal Medicine Department, Ain Shams University Hospitals, Cairo, Egypt.

Patients presenting with refractory GERD symptoms {unresponsiveness to 6–8 weeks' treatment with Proton Pump Inhibitors (PPIs) twice daily [13]} were selected from the Gastroenterology (GIT) outpatient clinic. During the study period (from August 2013 to January 2014); 73 patients presented to the GIT out patient clinic with refractory GERD symptoms. 58 patients agreed to participate in the present study but unfournately18 patients had to be excluded due to presence of one or more of the exclusion criteria.

All participants were subjected to the following: - history taking, through clinical examination including Ear, Nose and Throat (ENT) examination, Abdominal ultrasonography ,laboratory investigations including: liver function tests, renal function tests, complete blood count, serum Ig E level ,antinuclear antibodies, stool analysis and pregnancy test for female participants.

Upper GIT endoscopy was done for all participants with at least 3 biopsies taken from 2 different sites in the esophagus including the distal and either mid or proximal esophagus even if the esophagus appeared endoscopically normal. Gastric and duodenal biopsies were also taken along with esophageal biopsies [14]. After hematoxylin/ eosin staining, all biopsies were examined histopathologically by blinded gastrointestinal pathologists. An esophageal eosinophilic count $\geq$ 15/HPF, along with normal gastric and duodenal biopsies, substantiated the diagnosis of eosinophilic esophagitis [11].

Patients were excluded from the study if they had any of the following conditions: parasitic infestation, pregnant or nursing women, patients receiving any form of corticosteroid therapy including inhaled preparations, previous history of upper digestive tract surgery, decompensated chronic diseases , previous upper digestive endoscopy showing active peptic ulcer, esophageal diverticulum, Barrett's esophagus or esophageal obstruction, known causes of eosinophilia such as malignancy, collagen vascular disease, hypersensitivity reactions, vasculitis, sarcoidosis, hypoadrenalism and drug reactions,

This study was approved by the local ethical committee of the Ain Shams University hospitals and a written informed consent was obtained from each patient.

Statistical methods: Data were collected, coded and entered to a personal computer IBM compatible 2.6 GHz. Data were analyzed with the program statistical package for social science (SPSS) under windows version 11.0.1. The following tests were used: calculation of mean values, prevalence and percentage.

3. Results

Patients presenting with refractory GERD symptoms were selected from the GIT outpatient clinic of Ain Shams University hospitals. During the study period (from August 2013 to January 2014); 73 patients presented with refractory GERD symptoms. After applying the inclusion and exclusion criteria; only 40 patients were enrolled in the current study.

All included patients were adults with a mean age of 39.4 year ranging from 18 to 63 years. 45% of patients were males (18/40). 4 participants had essential hypertension, 7 participants had type II diabetes mellitus and 1 participant had bronchial asthma which was controlled by inhaled bronchodilators {salbutamol(short acting β agonist)} (table 1).

Table 1. *Study population characteristics.*

	Number	%
Gender		
Females	22/40	55
Males	18/40	45
Age		
<45 year	24/40	60
≥45 year	16/40	40
Comorbidities		
Hypertension	4/40	10
Diabetes mellitus	7/40	17.5
Asthma	1/40	2.5

%: percentage

Abdominal ultrasonography reports were unremarkable and results of all laboratory investigations were within normal reference ranges (including the peripheral blood eosinophilic count and serum Ig E level).

No esophageal lesion was observed on upper GIT endoscopy in 19 patients. 20 patients had erosive esophagitis (Los Angeles grade A&B) while undergoing treatment with PPIs and only one patient showed furrows and plaques which are strongly suggestive of eosinophilic esophagitis.

The esophageal biopsy outcomes, which included intraepithelial eosinophils counts in a high-power field (HPF), identified only one patient with eosinophilic esophagitis ($\geq$ 15 eosinophils /HPF). The other 39 patients presented a low eosinophilic count, with a maximum of 2 eosinophils /HPF, and no eosinophilic microabscesses were observed (table 2). The histopathological examination of gastric and duodenal biopsies of all participants was unremarkable.

Table 2. *Intraepithelial eosinophilic count.*

Patients / Eosinophils /HPF	Number	%
zero	30/40	75
1	5/40	12.5
2	4/40	10
≥ 15	1/40	2.5

HPF: High Power Field, %: percentage

The prevalence of eosinophilic esophagitis in this cohort was 2.5% (1/40). The affected participant was a 27 year old female patient who had a history of recurrent attacks of dysphagia (that was mainly for solids) and bronchial asthma (type 1 hypersensitivity reaction) for which she was treated with ,on demand, inhaled bronchodilators (short acting β agonist). The endoscopic examination of the affected participant showed furrows and plaques which are strongly suggestive of eosinophilic esophagitis.

4. Discussion

During GERD treatment, PPIs are the most common and effective class of drugs prescribed to heal erosive esophagitis; however, clinical trials have shown that 1/4 of patients with erosive GERD have persistent heartburn symptoms after 30 days of treatment [15]. Double doses and prolonged treatment have been described as factors that increase treatment efficacy [16]. Nevertheless, PPI therapeutic failure has become one of the greatest clinical challenges in the management of patients with GERD [17]. Causes for PPI therapeutic failure include incorrect drug administration and poor treatment adherence. Eosinophilic esophagitis has also been reported as a cause of GERD refractoriness [18].

While some authors reported a relatively high prevalence rate of eosinophilic esophagitis among patients with refractory GERD symptoms (15%) [5, 19], others reported very low rates (1-4%) [18, 20,21]. In accordance with the later group, the current study revealed a 2.5% (1/40) prevalence rate of eosinophilic esophagitis among adult Egyptian patients with refractory GERD symptoms.

This discrepancy, in prevalence rate, is related to many factors; first: differences in demographic data (i.e.: age group, gender predominance, race and ethnicity) of patients included in each study, second: the intraepithelial eosinophilic count at which the diagnosis of eosinophilic esophagitis was established (15 vs. 20), third: the complex interplay between eosinophilic esophagitis and GERD which can lead to many conflicting results [22]. It is plausible that acid reflux itself might cause or exacerbate an allergic inflammatory response. Proposed mechanisms whereby GERD can cause or exacerbate eosinophilic esophagitis include the following observations: (1) Acid increases eosinophils viability [23], (2) esophageal acid exposure induces the release of mast cell mediators [24] and (3) GERD is associated with dilated intercellular spaces in the squamous epithelium that might allow penetration of allergens. To further confuse matters, preliminary data suggest that PPI therapy might have anti-inflammatory effects beyond acid suppression [25]. On the other hand eosinophilic esophagitis was found to contribute to or causes GERD: The eosinophil inflammation may lead to an impaired function of the lower esophageal sphincter, induced either by acute inflammation or by fibrosis. This leads to secondary gastro-esophageal reflux. In this situation, the manifestation of the disease is dominated by symptoms and signs of eosinophilic esophagitis and, on endoscopy, typical signs of GERD are absent. However, patients present with some signs of GERD and pH-monitoring documents a pathologic reflux [26].

The cause of eosinophilic esophagitis is poorly understood, but allergic and immune-mediated mechanisms similar to those of asthma are implicated.

Between 50% and 80% of patients with eosinophilic esophagitis have a coexisting atopic disease such as atopic dermatitis, eczema, allergic rhinitis, or asthma, with a higher prevalence in children than in adults. Recent consensus recommendations devoted considerable attention to the role of allergy evaluation. In these patients, evidence suggests that allergy testing may predict response to therapy [27]. The finding of the current study goes in line with these data, patient who was found to have eosinophilic esophagitis had a long history of bronchial asthma (atopy or type 1 hypersensitivity reaction) for which she was treated with ,on demand, inhaled bronchodilators (short acting β agonist).

Of interest, there may be a seasonal variation of eosinophilic esophagitis, as suggested by a case report of a 21-year-old woman who had eosinophilic esophagitis that worsened symptomatically and histologically during the pollen season but resolved during winter [28]. All previous observations strongly point to the role aeroallergens may play in this disease.

The present clinical trial had few limitations. First, adherence to PPIs treatment was not directly supervised during the pre-inclusion period of the study. Second, different PPIs preparations were used (Omeprazole, Pantoprazole and Lansoprazole). Third, number of patients included in the present study is relatively small.

Finally and in conclusion, the low prevalence rate of eosinophilic esophagitis among the current small cohort of Egyptian patients with refractory GERD symptoms strongly mandates the search for additional data concerning the indications for esophageal biopsy in this subset of patients. The literature data and current study demonstrate that this information could include a history of personal or familial atopy, young age, concerns about dysphagia or food impaction in the esophagus and screening for endoscopic alterations, even subtle ones. Further studies should be conducted on larger scales of Egyptian patients with refractory GERD symptoms to draw a solid conclusion regarding the prevalence rate of eosinophilic esophagitis in this subset of patients.

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Disclosure

The authors have no financial disclosures or conflicts of interest to declare

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